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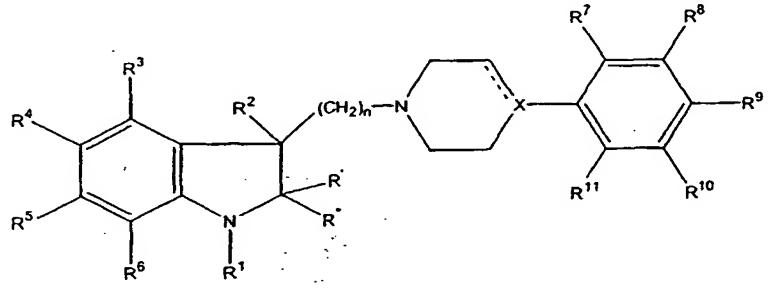
(54) **Title:** 3-INDOLINE DERIVATIVES USEFUL IN THE TREATMENT OF PSYCHIATRIC AND NEUROLOGIC DISORDERS



(I)

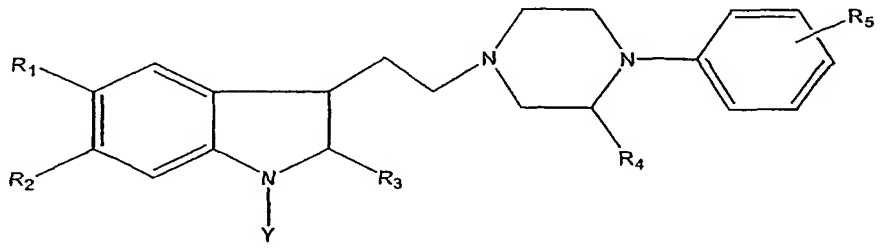
(57) **Abstract:** The present invention relates to the use of a compound having the general formula wherein R1 is acyl, thioacyl, trifluoromethylsulfonyl or R1 is a group R12SO2-, R12OCO- or R12SCO- wherein R12 is C1-6-alkyl, C2-6-alkenyl, C2-6-alkynyl, C3-8-cycloalkyl, C3-8-cycloalkyl-C1-6-alkyl or aryl, or R1 is a group R13R14NCO,- R13R14NCS-, wherein R13 and R14 are independently hydrogen, C1-6-alkyl, C2-6-alkenyl, C2-6-alkynyl, C3-8-cycloalkyl, C3-8-cycloalkyl-C1-6-alkyl or aryl, or R13 and R14 together with the N-atom to which they are linked form a pyrrolidinyl, piperidinyl or perhydroazepin group; n is 1-6;X is C, CH or N, and the dotted line emanating from X indicates a bond when X is C and no bond when X is N or CH;R', R'' and R2 are independently selected from hydrogen and C1-6-alkyl;R3-R11 are independently selected from hydrogen, halogen, cyano, nitro, C1-6-alkyl, C2-6-alkenyl, C2-6-alkynyl, C3-8-cycloalkyl, C3-8-cycloalkyl-C1-6-alkyl, amino, C1-6-alkylamino, di-(C1-6-alkyl)amino, C1-6-alkylcarbonyl, aminocarbonyl, C1-6-alkylaminocarbonyl, di-(C1-6-alkyl)aminocarbonyl, C1-6-alkoxy, C1-6-alkylthio, hydroxy, trifluoromethyl, trifluoromethylsulfonyl and C1-6-alkylsulfonyl; or a pharmaceutically acceptable acid addition salt thereof, for the manufacture of a medicament useful in the treatment of psychiatric and neurologic disorders, in particular psychoses.

3-INDOLINE DERIVATIVES USEFUL IN THE TREATMENT OF PSYCHIATRIC AND NEUROLOGIC DISORDERS

The present invention relates to a novel class of 3-indoline derivatives having affinity for the dopamine D_4 receptor. The compounds are useful in the treatment of certain psychiatric and neurologic disorders, in particular psychoses. The compounds also have affinity for the 5-HT_{2A} receptor.

Background of the Invention

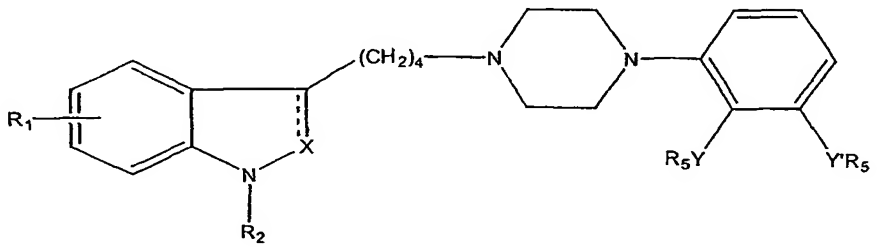
US patent No. 3,751,417 relates to 1-acyl-3-[2-(4-phenyl-1-piperazinyl)ethyl]indolines having the general formula



wherein R_1 is hydrogen, chloro, bromo, lower alkoxy, nitro, amino, acetamido or dimethylamino, R_2 is hydrogen, lower alkoxy or nitro, or R_1 and R_2 taken together is methylenedioxy, R_3 is hydrogen or methyl, R_4 is hydrogen or methyl, R_5 makes the phenyl-ring monosubstituted and is hydrogen, chloro, methoxy, methyl or trifluoromethyl and Y is benzoyl, p-chlorobenzoyl, p-nitrobenzoyl or lower alkanoyl. The compounds herein are said to be useful as tranquillisers and analgesics. It is known from clinical practice, that tranquillisers and analgesics are generally not adequate treatment of psychoses or anxiety disorders.

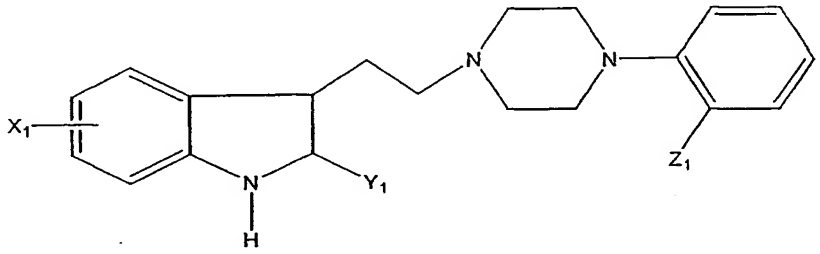
US 3,751,416 relates to similar compounds having a hydrogen in position 1 of the indoline ring. These compounds are also described as tranquillisers.

US 5,002,948 relates to compounds having the general formula



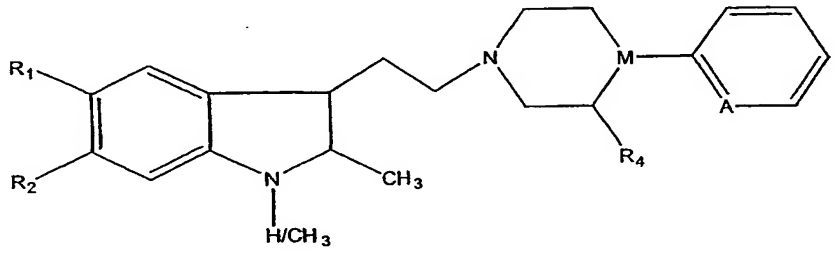
wherein R_1 is hydrogen, halogen, lower alkyl, lower alkenyl or trifluoromethyl, X is CH, CH_2, NH or CO, the dotted line indicates an optional bond, R_2 is hydrogen, lower alkyl, acyl etc., Y is O or S, Y' is H, O, S or CH_2 and R^5 is hydrogen, lower alkyl or alkenyl. The compounds are described as 5-HT_{1A} ligands being useful for the treatment of anxiety, depression, aggression, alcohol abuse and diseases related to the cardiovascular, the gastrointestinal and the renal system.

US 3,900,563 relates to compounds said to be useful for the treatment of psychotic disorders. The compounds disclosed herein have the general formula



wherein X_1 is 5,6-dimethoxy or 5,6-methylendioxy, Y_1 is hydrogen or methyl and Z_1 is hydrogen or methoxy. The compounds are shown in animals at doses of 10 mg/kg to induce catalepsy predicting extrapyramidal side effects. The compounds of the present invention do not induce catalepsy at doses of 20 mg/kg.

US 4,302,589 relates to substituted cis-2-methyl-3-[(piperazinyl) and (piperidino)ethyl]indolines having the general formula



wherein R_1 is fluoro, chloro, trifluoromethyl or methoxy, R_2 is hydrogen, chloro and methoxy, and M and A are carbon or nitrogen. These compounds are described as antipsychotics.

WO 92/22554 relates to certain 4-(phenylalkyl)piperidines having affinity for sigma receptors. Nothing is said about effect at dopamine D_4 receptors.

Dopamine D_4 receptors belong to the dopamine D_2 subfamily of receptors, which is considered to be responsible for the antipsychotic effects of neuroleptics. The side effects of neuroleptic drugs which primarily exert their effect via antagonism of D_2 receptors are known to be due to D_2 receptor antagonism in the striatal regions of the brain. However, dopamine D_4 receptors are primarily located in areas of the brain other than striatum, suggesting that antagonists of the dopamine D_4 receptor will be devoid of extrapyramidal side effects. This is illustrated by the antipsychotic clozapine which exerts higher affinity for D_4 than D_2 receptors and is lacking extrapyramidal side effects (Van Tol et al. *Nature* **1991**, *350*, 610; Hadley *Medicinal Research Reviews* **1996**, *16*, 507-526 and Sanner *Exp. Opin. Ther. Patents* **1998**, *8*, 383-393).

A number of D_4 ligands which were postulated to be selective D_4 receptor antagonists (L-745,879 and U-101958) have been shown to posses antipsychotic potential (Mansbach et al. *Psychopharmacology* **1998**, *135*, 194-200). However, recently it has been reported that these compounds are partial D_4 receptor agonists in various *in vitro* efficacy assays (Gazi et al. *Br. J. Pharmacol.* **1998**, *124*, 889-896 and Gazi et al. *Br. J. Pharmacol.* **1999**, *128*, 613-620). Furthermore, it was shown that clozapine, which is an effective antipsychotic, is a silent antagonists (Gazi et al. *Br. J. Pharmacol.* **1999**, *128*, 613-620).

Consequently, D_4 ligands which are partial D_4 receptor agonists or antagonists may have beneficial effects against psychoses.

Dopamine D_4 antagonists may also be useful for the treatment of cognitive deficits (Jentsch et al. *Psychopharmacology* **1999**, *142*, 78-84.

It has also been suggested that dopamine D_4 antagonists may be useful to reduce dyskinesia occurring as a result of the treatment of Parkinson's disease with L-dopa (Tahar et al. *Eur. J. Pharmacol.* **2000**, *399*, 183-186).

Furthermore, evidence for a genetic association between the "primarily inattentive" subtype of attention deficit hyperactivity disorder and a tandem duplication polymorphism in the gene encoding the dopamine D_4 receptor has been published (McCracken et al. *Mol. Psychiat.* **2000**, 5, 531-536). This clearly indicates a link between the dopamine D_4 receptor and attention deficit hyperactivity disorder and ligands affecting this receptor may be useful for the treatment of this particular disorder.

Various effects are known with respect to compounds which are ligands at the different serotonin receptor subtypes. As regards the 5-HT_{2A} receptor, which was previously referred to as the 5-HT_2 receptor, the following effects have been reported, e.g.:

Antidepressive effect and improvement of the sleep quality (Meert et al. *Drug. Dev. Res.* **1989**, *18*, 119), reduction of the negative symptoms of schizophrenia and of extrapyramidal side effects caused by treatment with classical neuroleptics in schizophrenic patients (Gelders *British J. Psychiatry* **1989**, *155* (suppl. 5), 33). Furthermore, selective 5-HT_{2A} antagonists could be effective in the prophylaxis and treatment of migraine (Scrip Report; "Migraine – Current trends in research and treatment"; PJB Publications Ltd.; May 1991) and in the treatment of anxiety (Colpart et al *Psychopharmacology* **1985**, *86*, 303-305 and Perregaard et al. *Current Opinion in Therapeutic Patents* **1993**, *1*, 101-128).

Some clinical studies implicate the 5-HT_2 receptor subtype in aggressive behaviour. Further, atypical serotonin-dopamine antagonist neuroleptics have 5-HT_2 receptor antagonistic effect in addition to their dopamine blocking properties and have been reported to possess anti-aggressive behaviour (Conner et al. *Exp. Opin. Ther. Patents.* **1998**, *8(4)*, 350-351).

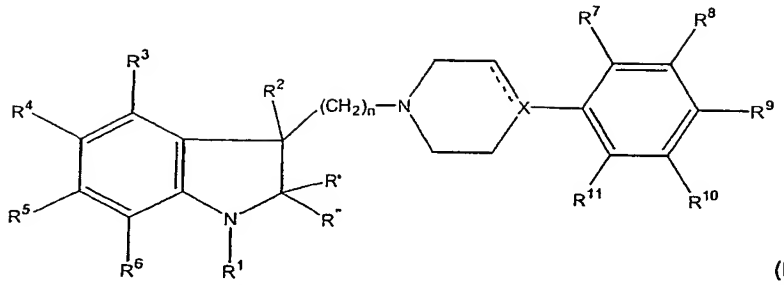
Recently, evidence has also accumulated, which support the rational for selective 5-HT_{2A} antagonists as drugs capable of treating positive symptoms of psychosis (Leysen et al. *Current Pharmaceutical Design* **1997**, *3*, 367-390 and Carlsson *Current Opinion in CPNS Investigational Drugs* **2000**, *2*(1), 22-24).

Accordingly, compounds with combined effects at dopamine D_4 and 5-HT_{2A} receptors may have the further benefit of improved effect on psychiatric symptoms in schizophrenic patients.

Summary of the Invention

The object of the present invention is to provide compounds which are partial agonists or antagonists at the dopamine D_4 receptor, in particular compounds with combined effects at the dopamine D_4 receptor and the 5-HT_{2A} receptor.

Thus, the present invention relates to the use of a compound having the general formula



(I)

wherein R^1 is acyl, thioacyl, trifluoromethylsulfonyl, or R^1 is a group $R^{12}SO_2$-, $R^{12}OCO$- or $R^{12}SCO$- wherein R^{12} is C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl or aryl, or R^1 is a group $R^{13}R^{14}NCO$-, $R^{13}R^{14}NCS$-, wherein R^{13} and R^{14} are independently hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl or aryl, or R^{13} and R^{14} together with the N-atom to which they are linked form a pyrrolidinyl, piperidinyl or perhydroazepin group;

n is 1-6;

X is C, CH or N, and the dotted line emanating from X indicates a bond when X is C and no bond when X is N or CH;

R', R'' and R^2 are independently selected from hydrogen and C_{1-6}-alkyl optionally substituted with a halogen atom; and

R^3-R^{11} are independently selected from hydrogen, halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, trifluoromethylsulfonyl and C_{1-6}-alkylsulfonyl;

or a pharmaceutically acceptable acid addition salt thereof, for the manufacture of a medicament useful in the treatment of as positive and negative symptoms of schizophrenia, other psychoses, anxiety disorders, such as generalised anxiety disorder, panic disorder, and obsessive compulsive disorder, depression, aggression, side effects induced by conventional anti-psychotic agents, migraine, cognitive disorders, dyskinesia induced by treatment with L-dopa, attention deficit hyperactivity disorder and in the improvement of sleep quality.

The invention also relates to compounds of formula (I) as defined above, but with the proviso that

(i) R^9 may not be hydrogen when R', R'', R^2-R^8, R^{10}-R^{11} are hydrogen, n is 2 and R^1 is acetyl;

(ii) R^9 may not be CF_3 or chloro, when R', R'', R^2-R^8, R^{10}-R^{11} are hydrogen, X is C or CH, n is 2 and R^1 is acetyl;

(iii) R^7 or R^{11} may not be methoxy when X is N, n is 2 or 4 and R^1 is acetyl; and

(iv) R^4 may not be methoxy.

or a pharmaceutically acceptable acid addition salt thereof.

According to a preferred embodiment, the present invention relates to the *S*-enantiomer of the compounds of formula (I) and the use thereof.

According to another embodiment, the present invention relates to compounds of formula (I) and the use thereof wherein R^7 and R^{11} are hydrogen. In a preferred embodiment, the present invention relates to such compounds of formula (I) and the use thereof wherein R^{10} is also hydrogen.

Another preferred group of compounds is that wherein X is CH and the dotted line is a bond.

In a particular preferred embodiment, the present invention relates to compounds wherein at least one of R^8 and R^9 is selected from halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, trifluoromethylsulfonyl and C_{1-6}-alkylsulfonyl.

In particular, R^8 and R^9 are identical or R^8 is hydrogen and R^9 is as defined above. In particular, R^8 and R^9 are identical and selected from halogen or alkyl, in particular methyl.

According to a more specific embodiment, the present invention relates to such compounds of formula (I) and the use thereof, wherein n is 2 or 3, preferably 2, and compounds wherein R^1 is acyl, in particular acetyl.

When R', R'' and R^2 is C_{1-6}-alkyl, they are preferably methyl.

R^4 is preferably hydrogen or halogen, in particular fluoro.

In a further embodiment, the present invention relates to compounds of formula (I) above wherein R', R'', R^2, R^3, R^5 and R^6 are hydrogen.

The compounds of the invention are partial agonists or antagonist at the dopamine D_4 receptors. The compounds also have affinity for the 5-HT_{2A} receptor.

Accordingly, the compounds of the invention are considered useful in the treatment of positive and negative symptoms of schizophrenia, other psychoses, anxiety disorders, such as generalised anxiety disorder, panic disorder and obsessive compulsive disorder, depression, aggression, side effects induced by conventional antipsychotic agents, dyskinesia induced by treatment with L-dopa, migraine, cognitive disorders, attention deficit hyperactivity disorder and in the improvement of sleep quality.

In particular, the compounds of the invention are considered useful in the treatment of positive and negative symptoms of schizophrenia without inducing extrapyramidal side effects.

In another aspect, the present invention provides a pharmaceutical composition comprising at least one compound of formula I as defined above or a pharmaceutically acceptable acid addition salt thereof in a therapeutically effective amount in combination with one or more pharmaceutically acceptable carriers or diluents.

In a further aspect, the present invention provides a method of treating the positive and negative symptoms of schizophrenia, other psychoses, anxiety disorders, such as generalised anxiety disorder, panic disorder, and obsessive compulsive disorder, depression, aggression, side effects induced by conventional anti-psychotic agents, migraine, cognitive disorders, dyskinesia induced by treatment with L-dopa, attention deficit hyperactivity disorder and in the improvement of sleep quality, comprising administration of a therapeutically acceptable amount of a compound of formula (I) as above.

Detailed Description of the Invention

The compounds of general formula I may exist as optical isomers thereof and such optical isomers as well as mixtures thereof are also embraced by the invention.

The term C_{1-6}-alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl and 2-methyl-1-propyl.

Similarly, C_{2-6}-alkenyl and C_{2-6}-alkynyl, respectively, designate such groups having from two to six carbon atoms, including one double bond and one triple bond respectively, such as ethenyl, propenyl, butenyl, ethynyl, propynyl and butynyl.

The terms C_{1-6}-alkoxy, C_{1-6}-alkylthio, C_{1-6}-alkylsulfonyl, C_{1-6}-alkylamino, C_{1-6}-alkylcarbonyl and the like designate such groups in which the alkyl group is C_{1-6} alkyl as defined above.

The term C_{3-8}-cycloalkyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms, such as cyclopropyl, cyclopentyl, cyclohexyl, etc.

Halogen means fluoro, chloro, bromo or iodo.

As used herein the term acyl refers to a formyl, C_{1-6}-alkylcarbonyl, arylcarbonyl, aryl-C_{1-6}-alkylcarbonyl, C_{3-8}-cycloalkylcarbonyl or a C_{3-8}-cycloalkyl-C_{1-6}-alkyl-carbonyl group and the term thioacyl is the corresponding acyl group in which the carbonyl group is replaced with a thiocarbonyl group. In the term C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-alkyl and C_{1-6}-alkyl are as defined above.

The term aryl refers to a carbocyclic aromatic group, such as phenyl or naphthyl, in particular phenyl, which may optionally be substituted with C_{1-6}-alkyl.

The acid addition salts of the compounds of the invention are pharmaceutically acceptable salts formed with non-toxic acids. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

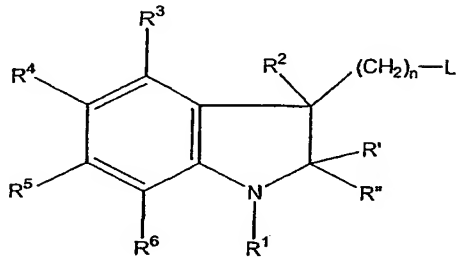
The pharmaceutical compositions of this invention, or those which are manufactured in accordance with this invention, may be administered by any suitable route, for example orally in the form of tablets, capsules, powders, syrups, etc., or parenterally in the form of solutions for injection. For preparing such compositions, methods well known in the art may be used, and any pharmaceutically acceptable carriers, diluents, excipients or other additives normally used in the art may be used.

Conveniently, the compounds of the invention are administered in unit dosage form containing said compounds in an amount of 0.01 to 100 mg.

The total daily dose is usually in the range of 0.05 - 500 mg, and most preferably in the range of 0.1 to 50 mg of the active compound of the invention.

The compounds of the invention may be prepared as follows:

1) Alkylating a piperazine, piperidine or tetrahydropyridine of formula III with an alkylating derivative of formula II:



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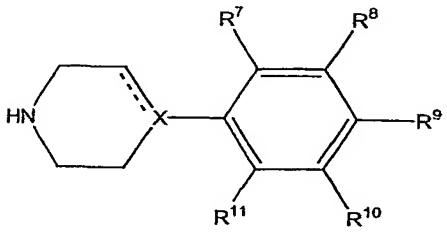
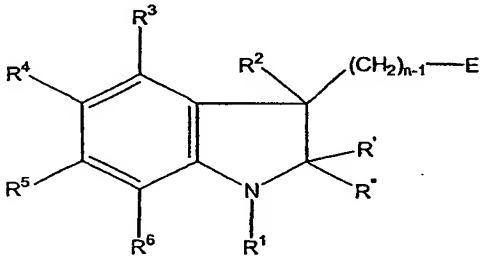


(III)

wherein R', R'', R^1-R^{11}, X, n and the dotted line are as previously defined, and L is a leaving group such as e.g. halogen, mesylate or tosylate;

2) Reductive alkylation of an amine of formula III with a reagent of formula IV:



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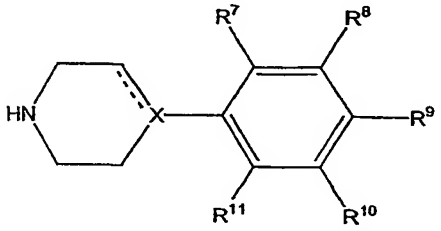
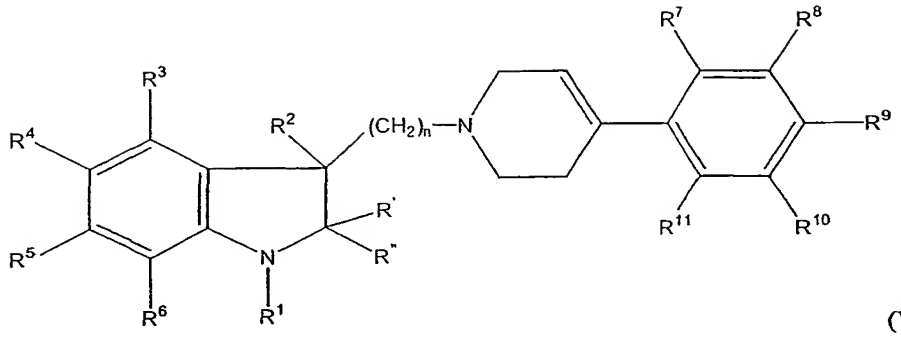


(III)

wherein R', R'', R^1-R^{11}, X, n and the dotted line are as previously defined and E is an aldehyde or an activated carboxylic acid;

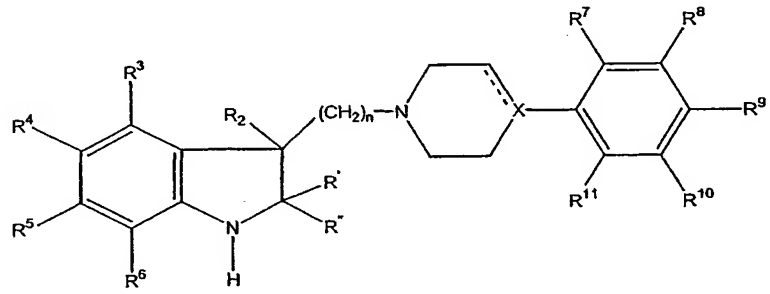
3) Reducing the double bond in the tetrahydropyridinyl ring in derivatives of formula V:



(V)

wherein R', R'', R^1-R^{11} and n are as previously defined; or

4) Acylating an amine of formula VI



(VI)

wherein R', R'', R^2-R^{11}, X, n and the dotted line are as previously defined, by the use of a carboxylic acid and a coupling reagent, an activated ester, an acid chloride, an isocyanate or by a two-step procedure by treatment with phosgene followed by addition of an amine;
whereupon the compound of formula I is isolated as the free base or a pharmaceutically acceptable acid addition salt thereof.

The alkylation according to method 1) is conveniently performed in an inert organic solvent such as a suitably boiling alcohol or ketone, preferably in the presence of an organic or inorganic base (potassium carbonate, diisopropylethylamine or triethylamine) at reflux temperature. Alternatively, the alkylation can be performed at a fixed temperature, which is different from the boiling point, in one of the above-mentioned solvents or in dimethyl formamide (DMF), dimethylsulfoxide (DMSO) or *N*-methylpyrrolidin-2-one (NMP), preferably in the presence of a base. The alkylating derivatives of formula II have been described in the literature (WO 98/28293), and the amines of formula III are commercially available or have been described in the literature.

The reductive alkylation according to method 2) is performed by standard literature methods. The reaction can be performed in two steps, e.g. coupling of amines of formula III with reagent of

formula IV by standard methods *via* the carboxylic acid chloride, activated esters or by the use of carboxylic acids in combination with a coupling reagents such as e.g. dicyclohexyl carbodiimide, followed by reduction of the resulting amide with lithium aluminium hydride or alane. The carboxylic acids of formula IV can be prepared by reduction of the corresponding indolecarboxylic acids by standard methods (see e.g. WO 98/28293).

The reduction of the double bond according to method 3) is generally performed by catalytic hydrogenation at low pressure (< 3 atm.) in a Parr apparatus, or by using reducing agents such as diborane or hydroboric derivatives as produced *in situ* from $NaBH_4$ in trifluoroacetic acid in inert solvents such as tetrahydrofuran (THF), dioxane or diethyl ether.

The acylation according to method 4) is conveniently performed by standard methods *via* the carboxylic acid chloride, activated esters or by the use of carboxylic acids in combination with coupling reagents such as e.g. dicyclohexyl carbodiimide. When the acylating reagent is carbamoyl chlorides or isocyanates, the acylation produces urea derivatives. The urea derivatives can also be prepared by a two-step procedure consisting of treatment with phosgene followed by addition of an amine.

The intermediate compounds of formula VI are prepared as described in methods 1) and 2).

Experimental Section

Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. Analytical LC-MS data were obtained on a PE Sciex API 150EX instrument equipped with IonSpray source and Shimadzu LC-8A/SLC-10A LC system. The LC conditions (C18 column 4.6 × 30 mm with a particle size of 3.5 µm) were linear gradient elution with water/acetonitrile/trifluoroacetic acid (90:10:0.05) to water/acetonitrile/trifluoroacetic acid (10:90:0.03) in 4 min at 2 mL/min. Purity was determined by integration of the UV trace (254 nm). The retention times, R_t, are expressed in minutes.

Mass spectra were obtained by an alternating scan method to give molecular weight information. The molecular ion, MH+, was obtained at low orifice voltage (5-20V) and fragmentation at high orifice voltage (100-200V).

Preparative LC-MS-separation was performed on the same instrument. The LC conditions (C18 column 20 × 50 mm with a particle size of 5 µm) were linear gradient elution with water/acetonitrile/trifluoroacetic acid (80:20:0.05) to water/acetonitrile/trifluoroacetic acid (5:95:0.03) in 7 min at 22.7 mL/min. Fraction collection was performed by split-flow MS detection.

^{1}H NMR spectra were recorded at 500.13 MHz on a Bruker Avance DRX500 instrument or at 250.13 MHz on a Bruker AC 250 instrument. Deuterated chloroform (99.8%D) or dimethyl sulfoxide (99.9%D) were used as solvents. TMS was used as internal reference standard. Chemical shift values are expressed in ppm-values. The following abbreviations are used for multiplicity of NMR signals: s=singlet, d=doublet, t=triplet, q=quartet, qui=quintet, h=heptet, dd=double doublet, dt=double triplet, dq=double quartet, tt=triplet of triplets, m=multiplet. NMR signals corresponding to acidic protons are generally omitted. Content of water in crystalline compounds was determined by Karl Fischer titration. For column chromatography silica gel of type Kieselgel 60, 230-400 mesh ASTM was used. For ion-exchange chromatography (SCX, 1 g, Varian Mega Bond Elut®, Chrompack cat. no. 220776). Prior use of the SCX-columns was pre-conditioned with 10% solution of acetic acid in methanol (3 mL).

Examples

Preparation of intermediates

A. Amines

4-(3,4-Dichlorophenyl)-3,6-dihydro-2*H*-pyridine

A mixture of butyllithium (1.6 M in hexane, 45 mL) and tetrahydrofuran (40 mL) was cooled down to –65-75 °C and subsequently added a solution of 4-bromo-1,2-dichlorobenzene (15 g) in tetrahydrofuran (25 mL). The resulting mixture was stirred at –65-75 °C for 1 h followed by the addition of ethyl 4-oxo-piperidine-1-carboxylate (11.5 g). The resulting mixture was stirred at –65-75 °C for 1 h followed by another 3 h at room temperature. The mixture was subsequently quenched by the addition of a saturated solution of ammonium chloride in water, and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give ethyl 4-(3,4-dichlorophenyl)-4-hydroxypiperidine-1-carboxylate (12.6 g). The residue was dissolved in trifluoroacetic acid (100 mL) and stirred at room temperature for 16 h. The solvent was removed *in vacuo*, and the residue was dissolved in a mixture of 4 M sodium hydroxide and ethanol and subsequently boiled under reflux for 48 h. The mixture was extracted with ethyl acetate, and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silicagel (eluent: ethyl acetate/4 M ammonia in methanol 1:1) to give the title compound (4.7 g).

4-(3,4-Dichlorophenyl)piperidine

A mixture of ethyl 4-(3,4-dichlorophenyl)-4-hydroxypiperidine-1-carboxylate (6.0 g), trifluoroacetic acid (50 mL) and triethylsilane (10 mL) was stirred at room temperature for 16 h. The mixture was

added water and ethyl acetate, and the phases were separated. The aqueous phase was extracted twice with ethyl acetate, and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* (5.8 g). The residue was dissolved in a mixture of 4 M sodium hydroxide and ethanol and subsequently boiled under reflux for 24 h. The mixture was extracted with ethyl acetate, and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silicagel (eluent: ethyl acetate/4 M ammonia in methanol 1:1) to give the title compound (1.8 g).

Preparation of the compounds of the invention

Example 1

1a, *(+)-1-[2-(1-Acetyl-2,3-dihydro-1H-indol-3-yl)ethyl]-4-(3,4-dimethylphenyl)piperazine,hydrochloride.*

A mixture of 1-(3,4-dimethylphenyl)piperazine (1.15 g), (+)-1-[2-(1-acetyl-2,3-dihydro-*1H*-indol-3-yl)ethylbromide (prepared in WO 98/28293) (1.3 g) and potassium carbonate (0.7 g) in acetonitrile (20 mL) were heated to 85 °C for 6 h. The mixture was cooled to room temperature , silicagel (7 g) added and the mixture evaporated *in vacuo* to give a white powder. The product was purified by flash chromatography on silicagel using as eluent ethylacetate/triethylamine (99:1). Fractions containing the product were pooled and evaporated *in vacuo*. The product was dissolved in tetrahydrofuran and converted to its hydrochloride by addition of HCl in diethylether (1.4 g). Mp 238-240°C. ^{1}H NMR (DMSO-d_6): 2.00-2.08 (m, 1H); 2.15 (s, 3H), 2.20 (s, 6H), 2.30 (m, 1H), 3.10-3.30 (m, 7H), 3.55 (m, 1H), 3.60 (m, 2H), 3.75 (m, 2H), 3.85 (m, 1H), 4.25 (m, 1H), 6.75 (d, 1H), 6.83 (s, 1H), 7.0 (t, 2H), 7.20 (t, 1H), 7.30 (d, 1H), 8.05 (d, 1H). MS m/z: 404 (MH+), 378.1.

The following compounds were prepared in a similar manner:

1b, *(+)-1-[2-(1-Acetyl-2,3-dihydro-1H-indol-3-yl)ethyl]-4-(4-methylphenyl)piperazine,hydrochloride* from 4-(4-methylphenyl)piperazine and (+)-1-[2-(1-acetyl-2,3-dihydro-*1H*-indol-3-yl)ethylbromide. Mp 217-220°C. ^{1}H NMR (DMSO-d_6): 2.00-2.08 (m, 1H); 2.17 (s, 3H), 2.23 (s, 3H), 2.30 (m, 1H), 3.10-3.30 (m, 7H), 3.55 (m, 1H), 3.60 (m, 2H), 3.75 (m, 2H), 3.85 (m, 1H), 4.25 (m, 1H), 6.90 (d, 2H), 7.05 (m, 3H), 7.20 (t, 1H), 7.30 (d, 1H), 8.05 (d, 1H). MS m/z: 404 (MH+), 364.0.

1c, *(+)-1-[2-(1-Acetyl-2,3-dihydro-1H-indol-3-yl)ethyl]-4-(4-methylphenyl)piperidine*
from 4-(4-methylphenyl)piperidine and (+)-1-[2-(1-acetyl-2,3-dihydro-*1H*-indol-3-yl)ethylbromide. Mp 112-114°C. ^{1}H NMR (DMSO-d_6): 1.60-1.80 (m, 5H); 2.00 (t, 3H), 2.17 (s, 3H), 2.23 (s, 3H), 2.40 (m, 3H), 3.00 (m, 2H), 3.45 (m, 1H), 3.60 (m, 2H), 3.80 (m, 1H), 4.20 (m, 1H), 7.00 (t, 1H), 7.10 (m, 4H), 7.20 (t, 1H), 7.30 (d, 1H), 8.05 (d, 1H). MS m/z: 404 (MH+), 364.1.

1d, *(+)-1-[2-(1-Acetyl-2,3-dihydro-1H-indol-3-yl)ethyl]-4-(3,4-dichlorophenyl)piperazine,hydrochloride* from 4-(3,4-dichlorophenyl)piperazine and (+)-1-[2-(1-acetyl-2,3-dihydro-*1H*-indol-3-yl)ethylbromide. Mp 184-186°C. ^{1}H NMR (DMSO-d_6): 2.00-2.08 (m, 1H); 2.15 (s, 3H), 2.30 (m, 1H), 3.10-3.30 (m, 7H), 3.55 (m, 1H), 3.60 (m, 2H), 3.75 (m, 2H), 3.85 (m, 1H), 4.25 (m, 1H), 7.0 (m, 2H), 7.20 (t, 1H), 7.25 (m, 1H), 7.30 (d, 1H), 7.43 (d, 1H), 8.05 (d, 1H). MS m/z: 404 (MH+), 417.9.

1e, *(+)-1-[2-(1-Acetyl-2,3-dihydro-1H-indol-3-yl)ethyl]-4-(4-bromophenyl)piperazine,hydrochloride* from 4-(4-bromophenyl)piperazine, hydrochloride and (+)-1-[2-(1-acetyl-2,3-dihydro-*1H*-indol-3-yl)ethylbromide.. ^{1}H NMR (DMSO-d_6): 2.00-2.08 (m, 1H); 2.17 (s, 3H), 2.30 (m, 1H), 3.10-3.30 (m, 4H), 3.55 (m, 1H), 3.60 (m, 2H), 3.70-4.00 (m, 6H), 4.25 (m, 1H), 6.90 (d, 2H), 7.05 (t, 1H), 7.20 (t, 1H), 7.30 (d, 1H), 7.48 (d, 2H), 8.05 (d, 1H). MS m/z: 404 (MH+), 427.9.

1f, *1-[2-(1-Acetyl-2,3-dihydro-1H-indol-3-yl)ethyl]-4-(3,4-dichlorophenyl)-3,6-dihydro-2H-pyridine, hydrochloride.*
from 4-(3,4-dichlorophenyl)-3,6-dihydro-2*H*-pyridine and (+)-1-[2-(1-acetyl-2,3-dihydro-*1H*-indol-3-yl)ethylbromide. ^{1}H NMR (DMSO-d_6): 1.95-2.10 (m, 1H); 2.20 (s, 3H); 2.25-2.35 (m, 1H); 2.70-2.80 (m, 1H); 2.80-2.95 (m, 1H); 3.15-3.30 (m, 3H); 3.45-3.55 (m, 1H); 3.60-3.75 (m, 1H); 3.75-3.85 (m, 1H); 3.85-3.90 (m, 1H); 3.95-4.05 (m, 1H); 4.25 (t, 1H); 6.35 (s, 1H); 7.05 (t, 1H); 7.20 (t, 1H); 7.35 (d, 1H); 7.50 (d, 1H); 7.65 (d, 1H); 7.75 (s, 1H); 8.05 (d, 1H). MS m/z: 415 (MH+).

1g, *1-[2-(1-Acetyl-2,3-dihydro-1H-indol-3-yl)ethyl]-4-(3,4-dichlorophenyl)piperidine, hydrochloride.*
from 4-(3,4-dichlorophenyl)piperidine and (+)-1-[2-(1-acetyl-2,3-dihydro-*1H*-indol-3-yl)ethylbromide. ^{1}H NMR (DMSO-d_6): 1.95-2.35 (m, 6H); 2.20 (s, 3H); 2.80-2.95 (m, 1H); 2.95-3.25 (m, 4H); 3.50 (broad s, 1H); 3.60 (d, 2H); 3.80-3.90 (m, 1H); 4.25 (t, 1H); 7.05 (t, 1H); 7.20 (t, 1H); 7.25 (d, 1H); 7.30 (d, 1H); 7.50 (s, 1H); 7.60 (d, 1H); 8.05 (d, 1H). MS m/z: 417 (MH+).

Pharmacological Testing

The compounds of the invention were tested in well recognised and reliable tests. The tests were as follows:

Inhibition of the binding of [^{3}H]YM-09151-2 to $D_{4.2}$ receptors

By this method, the inhibition by drugs of the binding of [^{3}H]YM-09151-2 (0.06 nM) to membranes of human cloned dopamine $D_{4.2}$ receptors expressed in CHO-cells is determined *in vitro*. The method is modified from NEN Life Science Products, Inc., technical data certificate PC2533-10/96.

Inhibition of the binding of [^{3}H]Ketanserin to 5-HT_{2A} receptors

The compounds were tested with respect to their affinity for 5-HT_{2A} receptors by determining their ability to inhibit binding of [^{3}H]Ketanserin (0.50 nM) to membranes from rat brain (cortex) *in vitro*. Method described in Sánchez et al. *Drug Dev. Res.* **1991**, *22*, 239-250. In table 1 below, the test results are shown:

Compound	IC_{50} (nM) or % inhib. at the D4-receptor	IC_{50} (nM) at the 5HT2A- receptor
1a	< 50/ 88	5.0
1b	< 50/ 88	15.
1c	< 50/ 76	17.
1d	< 50/ 86	21.
1e	< 50/ 95	17.
1f	13	27
1g	5.4	21

Table 1: Binding Data (% inhibition of binding at 50 nM)

The compounds of the invention have been found potently to inhibit the binding of tritiated YM-09151-2 to dopamine D_4 receptors. Further, the compounds bind potently to 5-HT_{2A} receptors.

The compounds have also been tested in a functional assay described by Gazi et al. in *Br. J. Pharmacol.* **1999**, *128*, 613-620. In this test, the compounds were shown to be partial agonists or antagonists at the dopamine D_4 receptors.

The compounds of the invention have also been tested in the following tests:

Inhibition of the binding of [^{3}H]Spiperone to rat dopamine D_2 receptors

The compounds were tested with respect to affinity for the dopamine D_2 receptor by determining their ability to inhibit the binding of [^{3}H]-spiperone to D_2 receptors by the method of Hyttel et al. *J. Neurochem,* **1985**, 44, 1615.

The compounds were found to have no substantial or only weak affinity for the dopamine D_2 receptor.

The compounds of the invention containing a tetrahydropyridine ring, i.e. compounds wherein X is CH and the dotted line indicates a bond, have particularly good pharmacokinetic properties.

Thus, the compounds of the invention are considered useful in the treatment of positive and negative symptoms of schizophrenia, other psychoses, anxiety disorders, such as generalised anxiety disorder, panic disorder, and obsessive compulsive disorder, depression, side effects induced by conventional antipsychotic agents, migraine, dyskinesia induced by treatment with L-dopa, attention deficit hyperactivity disorder and in the improvement of sleep quality. In particular, the compounds of the invention are considered useful in the treatment of positive and negative symptoms of schizophrenia without inducing extrapyramidal side effects.

Formulation Examples

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art.

For example: Tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tabletting machine. Examples of adjuvants or diluents comprise: corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvants or additives usually used for such purposes such as colourings, flavourings, preservatives etc. may be used provided that they are compatible with the active ingredients.

Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to desired volume,

sterilising the solution and filling it in suitable ampules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc. Typical examples of recipes for the formulation of the invention are as follows:

1) Tablets containing 5.0 mg of a compound of the invention calculated as the free base:

Compound	5.0 mg
Lactose	60 mg
Maize starch	30 mg
Hydroxypropylcellulose	2.4 mg
Microcrystalline cellulose	19.2 mg
Croscarmellose Sodium Type A	2.4 mg
Magnesium stearate	0.84 mg

2) Tablets containing 0.5 mg of a compound of the invention calculated as the free base:

Compound	0.5 mg
Lactose	46.9 mg
Maize starch	23.5 mg
Povidone	1.8 mg
Microcrystalline cellulose	14.4 mg
Croscarmellose Sodium Type A	1.8 mg
Magnesium stearate	0.63 mg

3) Syrup containing per millilitre:

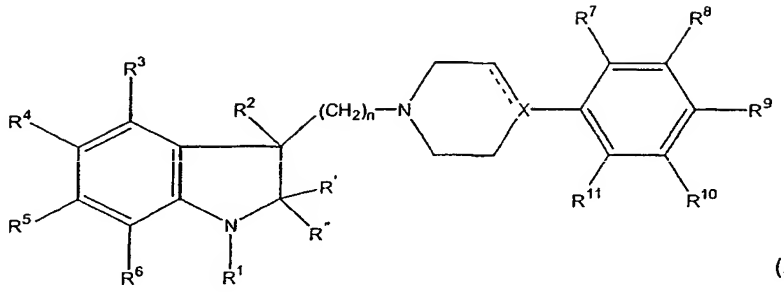
Compound	25 mg
Sorbitol	500 mg
Hydroxypropylcellulose	15 mg
Glycerol	50 mg
Methyl-paraben	1 mg
Propyl-paraben	0.1 mg
Ethanol	0.005 ml
Flavour	0.05 mg
Saccharin sodium	0.5 mg
Water	ad 1 ml

4) Solution for injection containing per millilitre:

Compound	0.5 mg
Sorbitol	5.1 mg
Acetic Acid	0.05 mg
Saccharin sodium	0.5 mg
Water	ad 1 ml

Claims

1. The use of a compound having the general formula



(I)

wherein R^1 is acyl, thioacyl, trifluoromethylsulfonyl, or R^1 is a group $R^{12}SO_2$-, $R^{12}OCO$- or $R^{12}SCO$- wherein R^{12} is C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl or aryl, or R^1 is a group $R^{13}R^{14}NCO$,- $R^{13}R^{14}NCS$-, wherein R^{13} and R^{14} are independently hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl or aryl, or R^{13} and R^{14} together with the N-atom to which they are linked form a pyrrolidinyl, piperidinyl or perhydroazepin group;

n is 1-6;

X is C, CH or N, and the dotted line emanating from X indicates a bond when X is C and no bond when X is N or CH;

R', R'' and R^2 are independently selected from hydrogen and C_{1-6}-alkyl optionally substituted with halogen; and

R^3-R^{11} are independently selected from hydrogen, halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, trifluoromethylsulfonyl and C_{1-6}-alkylsulfonyl;

or a pharmaceutically acceptable acid addition salt thereof, for the manufacture of a medicament useful in the treatment of positive and negative symptoms of schizophrenia, other psychoses, anxiety disorders, such as generalised anxiety disorder, panic disorder, and obsessive compulsive disorder, depression, aggression, side effects induced by conventional anti-psychotic agents, migraine,

cognitive disorders, dyskinesia induced by treatment with L-dopa, attention deficit hyperactivity disorder and in the improvement of sleep quality.

2. The use of a compound according to claim 1 which is in the form of the S-enantiomer.

3. The use of a compound according to claims 1-2 wherein R^7 and R^{11} are hydrogen.

4. The use of a compound according to claim 3 wherein R^{10} is hydrogen.

5. The compound of any of claims 1-4 wherein X is CH and the dotted line indicates a bond.

6. The use of a compound according to claims 1-4 wherein at least one of R^8 and R^9 are independently selected from halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, trifluoromethylsulfonyl and C_{1-6}-alkylsulfonyl.

7. The use of a compound according to claims 1- 6 wherein n is 2 or 3, preferably 2.

8. The use of a compound according to claims 1-7 wherein R^1 is acyl.

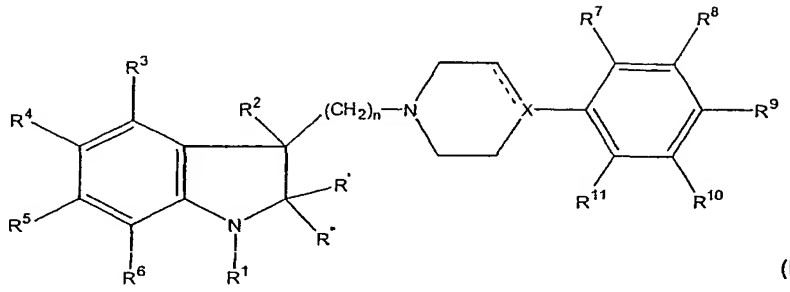
9. The use of a compound according to claim 8 wherein R^1 is acetyl.

10. The use of claims 1-9 wherein R^4 is hydrogen or fluoro.

11. The use of a compound according to claim 1 which is selected from
(+)-1-[2-(1-Acetyl-2,3-dihydro-*1H*-indol-3-yl)ethyl]-4-(3,4-dimethylphenyl)piperazine,
(+)-1-[2-(1-Acetyl-2,3-dihydro-*1H*-indol-3-yl)ethyl]-4-(4-methylphenyl)piperazine,
(+)-1-[2-(1-Acetyl-2,3-dihydro-*1H*-indol-3-yl)ethyl]-4-(4-methylphenyl)piperidine,
(+)-1-[2-(1-Acetyl-2,3-dihydro-*1H*-indol-3-yl)ethyl]-4-(3,4-dichlorophenyl)piperazine,
(+)-1-[2-(1-Acetyl-2,3-dihydro-*1H*-indol-3-yl)ethyl]-4-(4-bromophenyl)piperazine,
1-[2-(1-Acetyl-2,3-dihydro-1H-indol-3-yl)ethyl]-4-(3,4-dichlorophenyl)-3,6-dihydro-2H-pyridine,
and 1-[2-(1-Acetyl-2,3-dihydro-1H-indol-3-yl)ethyl]-4-(3,4-dichlorophenyl)piperidine,

or a pharmaceutically acceptable salt thereof.

12. An 3-indoline derivative of the general formula



(I)

wherein R^1 is acyl, thioacyl, trifluoromethylsulfonyl, or R^1 is a group $R^{12}SO_2$, $R^{12}OCO$- or $R^{12}SCO$- wherein R^{12} is C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl or aryl, or R^1 is a group $R^{13}R^{14}NCO$,- $R^{13}R^{14}NCS$-, wherein R^{13} and R^{14} are independently hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl or aryl, or R^{13} and R^{14} together with the N-atom to which they are linked form a pyrrolidinyl, piperidinyl or perhydroazepin group; and

n is 1-6;

X is C, CH or N, and the dotted line emanating from X indicates a bond when X is C and no bond when X is N or CH;

R', R'' and R^2 are independently selected from hydrogen and C_{1-6}-alkyl optionally substituted with halogen;

R^3-R^{11} are independently selected from hydrogen, halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonyl, aminocarbonyl, C_{1-6}-alkylaminocarbonyl, di-(C_{1-6}-alkyl)aminocarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, trifluoromethylsulfonyl and C_{1-6}-alkylsulfonyl;

with the proviso that

(i) R^9 may not be hydrogen when R', R'', R^2-R^8, R^{10}-R^{11} are hydrogen, n is 2 and R^1 is acetyl;

(ii) R^9 may not be CF_3 or chloro, when R', R'', R^2-R^8, R^{10}-R^{11} are hydrogen, X is C or CH, n is 2 and R^1 is acetyl;

(i) R^7 or R^{11} may not be methoxy when X is N, n is 2 or 4 and R^1 is acetyl; and

(iv) R^4 may not be methoxy;

or a pharmaceutically acceptable acid addition salt thereof.

13. A compound according to claim 12 which is in the form of the S-enantiomer.

14. A compound according to claims 12-13 wherein R^7 and R^{11} are hydrogen.

15. A compound according to claim 14 wherein R^{10} is hydrogen.

16. A compound of any of claims 12-15 wherein X is CH and the dotted line is a bond.

17. A compound according to claims 12-16 wherein at least one of R^8 and R^9 are selected from halogen, cyano, nitro, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, amino, C_{1-6}-alkylamino, di-(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonyl, C_{1-6}-alkoxy, C_{1-6}-alkylthio, hydroxy, trifluoromethyl, trifluoromethylsulfonyl and C_{1-6}-alkylsulfonyl.

18. A compound according to claims 12-17 wherein n is 2 or 3, preferably 2.

19. A compound according to claims 12-18 wherein R^1 is acyl.

20. A compound according to claim 19 wherein R^1 is acetyl.

21. A compound according to claims 12-20 wherein R^4 is hydrogen or fluoro and R', R'', R^2, R^3, R^5 and R^6 are hydrogen.

22. A compound according to claim 12 which is selected from
(+)-1-[2-(1-Acetyl-2,3-dihydro-*1H*-indol-3-yl)ethyl]-4-(3,4-dimethylphenyl)piperazine,
(+)-1-[2-(1-Acetyl-2,3-dihydro-*1H*-indol-3-yl)ethyl]-4-(4-methylphenyl)piperazine,
(+)-1-[2-(1-Acetyl-2,3-dihydro-*1H*-indol-3-yl)ethyl]-4-(4-methylphenyl)piperidine,
(+)-1-[2-(1-Acetyl-2,3-dihydro-*1H*-indol-3-yl)ethyl]-4-(3,4-dichlorophenyl)piperazine,
(+)-1-[2-(1-Acetyl-2,3-dihydro-*1H*-indol-3-yl)ethyl]-4-(4-bromophenyl)piperazine,
1-[2-(1-Acetyl-2,3-dihydro-1H-indol-3-yl)ethyl]-4-(3,4-dichlorophenyl)-3,6-dihydro-2H-pyridine,
and 1-[2-(1-Acetyl-2,3-dihydro-1H-indol-3-yl)ethyl]-4-(3,4-dichlorophenyl)piperidine,
or a pharmaceutically acceptable salt thereof.

23. A pharmaceutical composition characterised in that it comprises a compound of any of claims 12 to 22 in a therapeutically effective amount together with one or more pharmaceutically acceptable carriers or diluents.

24. A method of treating the positive and negative symptoms of schizophrenia, other psychoses, anxiety disorders, such as generalised anxiety disorder, panic disorder, and obsessive compulsive disorder, depression, aggression, side effects induced by conventional anti-psychotic agents, migraine, cognitive disorders, dyskinesia induced by treatment with L-dopa, attention deficit hyperactivity disorder and in the improvement of sleep quality comprising administration of a therapeutically acceptable amount of a compound according to any of claims 12 to 22.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 01/00835

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 401/06, C07D 403/06, C07D 209/14, A61K 31/4439, A61K 31/454, A61K 31/496, A61P 25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9222554 A1 (H. LUNDBECK A/S), 23 December 1992 (23.12.92), see particularly claim 1 and page 7, line 30 - page 8, line 3 --	1-24
X	EP 0376607 A1 (H. LUNDBECK A/S), 4 July 1990 (04.07.90), see claims and page 2, line 7 - line 8 --	1-24
X	US 3751417 A (GEORGE RODGER ALLEN, JR. ET AL), 7 August 1973 (07.08.73), see claims and column 1, line 42 - line 44 --	1-24
X	US 5418237 A (HENNING BÖTTCHER ET AL), 23 May 1995 (23.05.95), see claims --	1-24

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 March 2002	25 -03- 2002
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Nebil Gecer/EÖ Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 01/00835

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0736525 A1 (MERCK PATENT GMBH), 9 October 1996 (09.10.96), see claims and page 5, line 45 - line 51	1-24
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X	US 4302589 A (WILLIAM J. FANSHWAVE ET AL), 24 November 1981 (24.11.81), see claims and abstract	1-24
	--	
X	US 3900563 A (GEORGE RODGER ALLEN, JR. ET AL), 19 August 1975 (19.08.75), see claims	1-24
	--	
X	WO 9421630 A1 (MERCK SHARP & DOHME LIMITED), 29 Sept 1994 (29.09.94), see particularly claim 2 and page 2, line 16 - line 25	1-24
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK01/00835

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 24
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

International application No.
PCT/DK01/00835

Claim 24 relates to a method of treatment of the human or animal body by surgery or by therapy/a diagnostic method practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/01/02

International application No.
PCT/DK 01/00835

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9222554 A1	23/12/92	AT 170523 T	15/09/98
		AU 664557 B	23/11/95
		AU 1984892 A	12/01/93
		CA 2111204 A	23/12/92
		CZ 289479 B	16/01/02
		CZ 9302726 A	13/04/94
		DE 69226867 D,T	12/05/99
		DK 15792 D	00/00/00
		DK 593511 T	31/05/99
		EP 0518805 A	16/12/92
		EP 0593511 A,B	27/04/94
		SE 0593511 T3	
		EP 0853085 A	15/07/98
		EP 0859004 A	19/08/98
		ES 2123557 T	16/01/99
		FI 108137 B	00/00/00
		FI 935558 A	10/12/93
		FI 992135 A	04/10/99
		HK 1009272 A	00/00/00
		HU 210869 B	28/08/95
		HU 9500094 A	29/05/95
		IE 921882 A	16/12/92
		IL 102155 D	00/00/00
		JP 2834577 B	09/12/98
		JP 3203230 B	27/08/01
		JP 6508360 T	22/09/94
		JP 10316659 A	02/12/98
		JP 11001475 A	06/01/99
		KR 212231 B	02/08/99
		MX 9205117 A	01/08/93
		NO 306497 B	15/11/99
		NO 310275 B	18/06/01
		NO 934494 A	11/02/94
		NO 994487 A	11/02/94
		NO 994488 A	11/02/94
		NZ 243065 A	26/07/95
		RU 2142952 C	20/12/99
		SG 48237 A	17/04/98
		SK 140993 A	09/11/94
		SK 280899 B	12/09/00
		SK 281747 B	10/07/01
		SK 281748 B	10/07/01
		US 5665725 A	09/09/97
		US 5807871 A	15/09/98
		US 6031099 A	29/02/00
		US 6207677 B	27/03/01
		BR 1100954 A	01/08/00
		DK 112991 D	00/00/00
		ZA 9204274 A	31/03/93
		DK 113191 D	00/00/00

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/01/02

International application No.
PCT/DK 01/00835

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0376607 A1	04/07/90	SE 0376607 T3	
		AT 102184 T	15/03/94
		AU 637991 B	17/06/93
		AU 4719889 A	05/07/90
		CA 2006356 A	28/06/90
		DE 68913487 D,T	04/08/94
		DK 169266 B	26/09/94
		DK 645689 A	29/06/90
		ES 2062050 T	16/12/94
		FI 93005 B,C	31/10/94
		FI 896300 D	00/00/00
		GB 8830312 D	00/00/00
		IE 62668 B,L	22/02/95
		IL 92990 A	24/01/95
		JP 2225460 A	07/09/90
		JP 2895121 B	24/05/99
		NO 174772 B,C	28/03/94
		NO 895281 D	00/00/00
		NZ 231855 A	25/02/92
		PT 92728 A,B	29/06/90
		US 5002948 A	26/03/91
		ZA 8909960 A	28/11/90
US 3751417 A	07/08/73	NONE	
US 5418237 A	23/05/95	AT 170837 T	15/09/98
		AU 655623 B	05/01/95
		AU 1033292 A	30/07/92
		CA 2059708 A	23/07/92
		CS 9200163 A	12/08/92
		CZ 281566 B	13/11/96
		DE 4101686 A	23/07/92
		DE 59209487 D	00/00/00
		DK 496222 T	07/06/99
		EP 0496222 A,B	29/07/92
		SE 0496222 T3	
		ES 2123521 T	16/01/99
		HK 1011991 A	00/00/00
		HU 67028 A	30/01/95
		HU 220061 B	28/10/01
		HU 9200194 D	00/00/00
		IE 920181 A	29/07/92
		JP 4334366 A	20/11/92
		KR 225702 B	15/10/99
		MX 9200239 A	01/07/92
		PT 100041 A,B	31/03/93
		SK 279363 B	07/10/98
		ZA 9200451 A	28/10/92

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/01/02

International application No.
PCT/DK 01/00835

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0736525 A1	09/10/96	SE 0736525 T3	
		AT 194595 T	15/07/00
		AU 709708 B	02/09/99
		AU 5040896 A	17/10/96
		BR 9601275 A	13/01/98
		CA 2173418 A	06/10/96
		CN 1072209 B	03/10/01
		CN 1137036 A	04/12/96
		CZ 289449 B	16/01/02
		CZ 9600964 A	16/10/96
		DE 19512639 A	10/10/96
		DE 59605568 D	00/00/00
		DK 736525 T	30/10/00
		ES 2150039 T	16/11/00
		GR 3034514 T	29/12/00
		HU 9600876 A	28/09/98
		JP 9151174 A	10/06/97
		NO 305903 B	16/08/99
		NO 961346 A	07/10/96
		PL 313632 A	14/10/96
		PT 736525 T	29/12/00
		SI 736525 T	00/00/00
		SK 40396 A	06/11/96
		SK 281457 B	12/03/01
		TR 970156 A	00/00/00
		US 6310068 B	30/10/01
		ZA 9602768 A	13/11/96
US 4302589 A	24/11/81	NONE	
US 3900563 A	19/08/75	NONE	
WO 9421630 A1	29/09/94	AT 160779 T	15/12/97
		AU 685090 B	15/01/98
		AU 6214094 A	11/10/94
		CA 2156838 A	29/09/94
		DE 69407174 D,T	02/07/98
		EP 0689539 A,B	03/01/96
		ES 2110225 T	01/02/98
		GB 9305623 D	00/00/00
		JP 8512284 T	24/12/96
		US 5780475 A	14/07/98